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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/417,386      | 10/13/99    | ROTHBERG             | J 15966-539         |

HM12/1013  
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EXAMINER

TAYLOR, J

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1656

8

DATE MAILED: 10/13/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

|                              |                               |                                 |  |
|------------------------------|-------------------------------|---------------------------------|--|
| <b>Office Action Summary</b> | Application No.<br>09/417,386 | Applicant(s)<br>ROTHBERG ET AL. |  |
|                              | Examiner<br>Janell E. Taylor  | Art Unit<br>1656                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

- 1) ☐ Responsive to communication(s) filed on 01 August 2000.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 21-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some \* c) ☐ None of the CERTIFIED copies of the priority documents have been:
1. ☐ received.
2. ☐ received in Application No. (Series Code / Serial Number) \_\_\_\_\_.
3. ☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

- |  |  |
|--|--|
| 15) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                             | 18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 16) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 17) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 20) <input type="checkbox"/> Other:  |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that no serious burden would be placed upon the Examiner by searching both subject matters. This is not found persuasive because Group II adds a new element to the claims, that is, a terminal cap structure. This creates a new search, and because the claims of Group I are able to function without the further invention of Group II, they are considered to be separate inventions requiring separate searches. The requirement is still deemed proper and is therefore made FINAL.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 20 is drawn to a method for equalizing the representation of nucleic acids in a population of nucleic acids, comprising: a) providing a population of nucleic acid sequences wherein one nucleic acid is present in higher levels than another; partitioning the population into subpopulations; and comparing the levels of the two nucleic acids to make sure they are normalized. However, this is a method for detecting whether two populations are equalized, not a method for equalizing. There are no steps which recite how the equalization takes place. This is

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considered a gap between the steps, because the steps go from providing two populations which are present at different levels to comparing levels which should be normalized, but there is no step reciting how that normalization takes place. Correction is required.

***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al. (Science, Vol. 252, pages 1651-1656, June 1991).

The claims are drawn to a method of screening a population of nucleic acids for a novel sequence, the method comprising: providing a population of nucleic acid sequences; partitioning said population into one or more subpopulations of nucleic acids; identifying a first nucleic acid sequence in the subpopulation of nucleic acid sequences; and comparing the first nucleic acid sequence to a reference nucleic acid sequence or sequences, wherein the absence of the first nucleic acid sequence in the reference nucleic acid or nucleic acid sequences indicates the first nucleic acid is a novel nucleic acid sequence. Further embodiments are that the DNA population is a cDNA population derived from a population of RNA molecules.

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Adams et al. teach a method for complementary DNA sequencing of EST's (expressed sequence tags). Adams et al. teaches "Subtractive hybridization has been used by researchers to reduce the population of highly represented sequences in a cDNA library by selectively removing sequences shared by another library." (*partitioning said population into one or more subpopulations of nucleic acids*). Adams also teaches "Initially, EST sequences were examined for similarities in the GenBank nucleic acid database. ESTs without exact GenBank matches were translated in all six reading frames, and each translation was compared with the protein sequence database Protein Information Resource (PIR) and the ProSite protein motif database....The BLAST programs contain a rapid database-searching algorithm that searches for local areas of similarity between two sequences and then extends the alignments on the basis of defined match and mismatch criteria." (*comparing the first nucleic acid sequence to a reference nucleic acid sequence or sequences*). (Page 1653).

Therefore, Adams et al. teach all of the limitations of the above specified claims.

***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 4-6 and 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al. in view of Aggarwal et al. (US Patent 5,824,509).

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The claims are drawn to the method of claim 1, but further comprising the cDNA population being derived from the 5' end, or the interior of the molecule, or the 3' end. Further embodiments are: digesting the cDNA molecules with a restriction enzyme, ligating adapter oligonucleotides to the termini, then amplifying the products, and separating them by gel electrophoresis. Also disclosed is comparing the size of products to a reference, and reamplifying the recovered products, and recombining them to a reference. Further embodiments include inserting the ligated adapter into a cloning vector to form a vector-insert, transforming the vector into a suitable host, culturing the transformed host under conditions allowing for replication of the vector-insert, recovering the vector insert from the host, digesting the vector-insert with one or more restriction enzymes, and comparing the size of the insert to references. And claim 20, an independent claim, teaches a method for equalizing the representation of nucleic acids in a population of nucleic acids, comprising: a) providing a population of nucleic acid sequences wherein one nucleic acid is present in higher levels than another; partitioning the population into subpopulations; and comparing the levels of the two nucleic acids to make sure they are normalized.

As discussed above, Adams et al. teaches "Subtractive hybridization has been used by researchers to reduce the population of highly represented sequences in a cDNA library by selectively removing sequences shared by another library." Adams also teaches "Initially, EST sequences were examined for similarities in the GenBank nucleic acid database. ESTs without exact GenBank matches were translated in all six reading frames, and each translation was compared with the protein sequence database Protein

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Information Resource (PIR) and the ProSite protein motif database....The BLAST programs contain a rapid database-searching algorithm that searches for local areas of similarity between two sequences and then extends the alignments on the basis of defined match and mismatch criteria." (Page 1653).

Adams et al. do not teach that the cDNA is derived from a certain end, or the use of a ligating adapter, or separating by gel electrophoresis, or using a vector and a host, or normalizing populations.

Aggarwal et al. teach "RNA was isolated from a culture...Reverse transcriptase was used to make a cDNA copy of the messenger RNA by standard methods...In order to insert the cDNA into a vector the ends were ligated to an adapter or linkers so as to create 5' and 3' restriction enzyme sites...The oligonucleotide was ligated to the cDNA and the cDNA reisolated by polyacrylamide gel electrophoresis...the ligation mixture was used to transfect E. coli..." (Col. 21, example 2).

In regards to the end from which the cDNA population is derived, it would have been obvious to one of ordinary skill in the art that cDNA was derivable from any part of the RNA fragment, and this was well known in the art.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Adams et al. and Aggarwal et al. This is because it would have been obvious to compare a sequence with a reference sequence in order to determine if they were the same or if the subject was a novel nucleic acid. It was well known in the art to ligate an adapter sequence on the end of a cDNA molecule so that it may be used in a vector and later excised. It was also well known in the art to use gel electrophoresis to

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separate segments and compare them, and reamplify them. Therefore, it would have been obvious to combine these teachings because they were all well known and standard practice in the art, and it would have been useful to combine them so that a reference nucleic acid would have been comparable to the sequence at hand.

### ***Summary***

Claim 20 is rejected under 35 U.S.C. 112, second paragraph. Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b). Claims 4-6 and 8-20 are rejected under 35 U.S.C. 103(a). No claims are free of the prior art.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor, whose telephone number is (703) 305-0273.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Any inquiries of a general nature relating to this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 305-3014 or 305-4227. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor

October 5, 2000

  
W. Gary Jones  
Supervisory Patent Examiner  
Technology Center 1600

10/10/00